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Commentary

Tenofovir Activating Kinases May Impact the Outcome of HIV Treatment and Prevention

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Tenofovir (TFV), an acyclic nucleoside phosphonate analogue of 2′-deoxyadenosine, remains a first-line choice for the treatment of HIV infections under its prodrug form (i.e. tenofovir disoproxil fumarate, TDF). During the last decade, the use of TFV in pre-exposure prophylaxis (PrP) was first investigated as a vaginal microbicide gel (Mayer et al., 2006). More recently, rectal microbicide preparations and oral TDF alone or in combination with emtricitabine have been evaluated in PrP (Marrazzo et al., 2015), opening a new era in the fight against HIV. Clinical studies using TFV-based regimens in PrP provided inconsistent results, which have been primarily explained by poor adherence.

The study by Lade et al. (2015) explored whether differences in the mechanism of TFV activation in peripheral blood mononuclear cells (PBMCs), vaginal and colorectal tissues exist. Also, they examined whether genetic variation in the nucleotide kinases that activate the drug could be responsible for the discrepant results observed in PrP studies using TFV-based regimens.

To be active, TFV requires two successive phosphorylation catalyzed by cellular kinases. Then, its active diphosphate form (TFV-DP) targets the HIV reverse transcriptase leading to inhibition of viral replication. The first step of TFV activation is substrate-specific and requires phosphorylation by a cellular adenylate kinase (AK). The isoform AK2 is known to be localized in the mitochondrial intermembrane space and to catalyze TFV phosphorylation in a more efficient manner than its cytoplasmic counterpart AK1.

Lade et al. (2015) found that AK2 activates TFV to TFV-MP in PBMCs and vaginal and colon tissues from healthy, HIV-uninfected donors that were not administered with the drug. Two questions rise regarding an AK2-dependent activation of TFV. The first issue is whether AK2 exists as a cytosolic form in PBMCs and in vaginal and colorectal tissues. Several studies reported the existence of small amounts of AK2 in the cytosol of porcine and rat tissues (Nobumoto et al., 1998; Watanabe et al., 1979). In contrast, Jurkat cells, a human leukemic T cell line, showed the absence of AK2 in the cytosol (Kohler et al., 1999). If small amounts of AK2 are present in the cytosol, will these low AK2 levels produce sufficient TFV-MP to afford anti-HIV activity? If AK2 is only expressed in the mitochondrial intermembrane space, then the activation of TFV will be performed exclusively in the mitochondria. Hence, the second issue is that TFV activation in the mitochondria will necessitate export of the phosphorylated form (TFV-MP or TFV-DP) into the cytosol via an active transport in order to exert its anti-HIV activity and to avoid mitochondrial toxicity. Several reports described TFV mitochondrial toxicity in renal proximal tubular cells (Lebrecht et al., 2009), while others showed no toxicity in HepG2 cells and skeletal muscle cells (Birkus et al., 2002). Furthermore, it is known that the use of TFV can be associated, in some cases, with renal dysfunction and Fanconi syndrome. Therefore, it will be interesting to investigate in PBMCs, vaginal and colorectal tissues the localization of AK2 and the mitochondrial transporter(s) that might contribute to the export of TFV-MP and/or TFV-DP.

The second step of TFV activation involves kinases that recognize a wide range of substrates. Several nucleoside diphosphate kinases (NDPKs) can be responsible for the production of TFV-DP, including NDPK1, NDPK2, pyruvate kinase (PK), phosphoglycerate kinase (PGK), and creatine kinase (CK). Interestingly, the analysis by Lade and colleagues points to a role of PK in the conversion of TFV-MP to TFV-DP in PBMCs and vaginal tissue, while CK appeared to be responsible for the formation of TFV-DP in colon tissue. These findings are in agreement with enzymatic results reported by Varga et al. showing a CK-mediated phosphorylation of TFV-MP, without excluding a possible role for PK (Varga et al., 2013).

In their study, Lade et al. (2015) also highlight the notion that genetic variants within the nucleotide kinases that exhibit enzymatic activity towards TFV exist, which may influence drug pharmacokinetics and drug efficacy. By means of next-generation targeted sequencing of the Microbicide Trials Network MTN-001 clinical samples, they identified genetic variants in the genes encoding for the kinases involved in TFV activation. The functional impact of the detected genetic variants was predicted using in silico tools, therefore, their attempt to correlate the detected genetic variants to enzyme function is purely predictive.

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Because the relative frequency of the genetic variants detected among the participants of the MTN-001 study was low, the authors could not make strong correlations with published TFV pharmacokinetic data (Hendrix et al., 2013). Further research should focus on the expression of recombinant enzymes produced by site-directed mutagenesis in order to test the impact of the identified genetic variants on TFV activation. Also, future studies that would correlate genotype with TFV pharmacology are also important in order to predict clinical outcomes.

Taken together, the study reported in this issue of E-BioMedicine (Lade et al., 2015) is an important step in two new concepts. First, the activation of TFV is tissue specific due to differential nucleotide kinase expression and activity which may be linked to potential differential pharmacology of TDF. Second, genetic variants of the kinases that activate TFV could impact TFV activation, influencing the efficacy of TFV in the prophylaxis and treatment of HIV.

Disclosure

The authors declared no conflicts of interest.

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